Exhibit E

7

Oils and Fats Group International Lecture

The year of the fish oils

ROBERT G ACKMAN

The Society of Chemical Industry (SCI) has been well aware of the importance of fish oils over the years and as long ago as 1928 an excellent review anticipated some of the needs of today.[1] Among these, is the question of stearin formation being better with Japanese sardine oil from southern waters than from northern waters. Table 1 provides part of the answer. It is clear that at iodine values of 150 or less, there is a relatively low percentage of saturated acids, and correspondingly a high proportion of two specific monoenes, 20:1 and 22:1. The latter are, in most fish oils, of exogenous origin[2] and tend to occur in the 3 position of fish oil triacylglycerols.[3] When they are not present there may be endogenous palmitic acid inserted in this portion and hence we have the paradox of more saturated acids in very highly unsaturated oils.

The triglyceride distribution in the Japanese sardine oil of Fig 1,[4] may make it clearer why a sharp stearin separation should occur with this oil. Such stearin formation is an economical first step in enriching fish oils in the two long-chain polyunsaturated fatty acids (PUFA) of current biomedical interest, respectively EPA or 20:5n-3 (eicosapentaenoic acid) and DHA or 22:6n-3 (docosahexaenoic acid). These may be regarded as either nutritional supplements, or as therapeutic agents inhibiting a variety of pathological conditions in man[5-7] and are popularly known as the 'omega-3' fatty acids.

Are all fish oils equal?

Marine bivalve invertebrates do not need much fat, using glycogen as their energy reserves. Among the zooplanktonic crustacea, copepods store wax esters as well as triglycerides,[2] and this fat is readily accumulated, after oxidation of fatty alcohols to fatty acids, by fish feeding on copepods.[8,9] Oils from capelin, herring, mackerel, anchovies and sardines are such fish oils. To make fish oil from the bodies of fatty fish essentially requires only the processes of cooking and pressing, followed by as much refining as is necessary for the end product.[10]

Table 1 shows how EPA and DHA naturally make up at most only about 25 per cent of fish and fatty acids. At this time of interest in therapy with fish oils or concentrates, it is useful to refer to Table 2. By judicious winterisation and blending, or by use of other techniques, for example solvent crystallisation and/or molecular distillation, concentrations of EPA and DHA in fish oils totalling 300 mg/g are readily obtained. This is usually found as a 2:1 ratio of EPA to DHA, the proportions being common in many marine oils from temperate and colder waters.[11,12] To achieve an oil concentration of EPA and DHA totalling above 300 mg/g is often rather difficult. Table 2 shows that the products of 500 mg/g are commonly in the form of ethyl or methyl esters of fatty acids.

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The **Oils and Fats International Lecture** was established in 1964 from the investment of a capital sum donated to the SCI for the purpose. The lecture is delivered before the Oils and Fats Group of the Society once every two years or as may be decided.

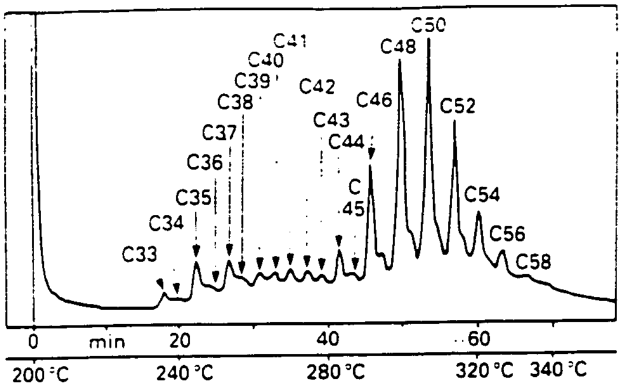


Fig 1 Unusual fish triglycerides found in muscle oil from Japanese sardine *(Sardinops melanosticta)*. The C_{33}-C_{44} grouping is not commonly found in marine fish oil triglycerides[4]

Enriching the omega-3 fatty acids

Information on such a concentrate was published in the SCI's Journal of the Science of Food and Agriculture, in 1964 at a time when total polyunsaturation of fats was being promoted to reduce serum cholesterol.[13] The commercial product, called 'Ethive', had 26 per cent EPA and 22 per cent DHA and was made from cod liver oil nominally containing 10 per cent and 7 per cent respectively of these two fatty acids. Attainment of concentrations of EPA and DHA similar to those of 'Ethive' from almost any fish oil is possible using urea complexing[14,15] to eliminate all straight chain saturated acids and also most monoethylene fatty acids.

It is important to note that most marine fish oils from northern latitudes contain very low levels of omega-6 fatty acids, typically 1-2 per cent of linoleic acid (18:2n-6) and 0.5-1.0 per cent of arachidonic acid (20:4n-6).[11] When urea complexing (Fig 2) or similar enrichment techniques are applied, the former may be eliminated partly but the latter can be co-concentrated in parallel with EPA, while gamma-linolenic acid (20:3n-6) may well be unchanged. Similarly, among the other omega-3 fatty acids alpha-linolenic (18:3n-3) will probably be unchanged or slightly concentrated, but 18:4n-3, 20:4n-3 and 22:5n-3 will all be enriched to nearly the same extent as EPA. The latter group of minor fatty acids can total 4-6 per cent in many fish oils,[11] and therefore it is not

Table 1 **Some major marine oils of commerce, with approximate iodine values, weight percentages of saturated acids, of 20:1 + 22:1, and of EPA + DHA**

		IV	%SAT	%(20:1 + 22:1)	%(EPA + DHA)
Body oils:	herring (Atlantic)	125	19	35	14
	capelin	125	18	36	11
	redfish	125	21	36	9
	herring (Pacific)	140	34	10	7
	sand launce	140	24	27	17
	mackerel	150	27	38	15
	salmon (Pacific)	150	26	17	19
	sardine	160	30	8	24
	menhaden	162	32	2	20
	anchovy	181	30	3	26
	pilchard	185	28	5	26
Liver oils:	cod (Atlantic)	165	21	13	24
	pollock (Alaska)	160	18	30	17
	squid (Pacific)	180	21	17	28
Other:	salmon egg (Pacific)	210	?	?	≈38[a]
	seal (Atlantic)	150	14	17	14

[a]The calculated total polyunsaturated fatty acids are 48 per cent by weight

Table 2 **Contents of EPA, DHA, cholesterol and tocopherol in some retail fish oil nutritional supplements sold in capsule form, with type product and label information, on the basis of 1000 mg capsules**

	Fatty Acid EPA mg/g	Fatty Acid DHA mg/g	Product type	Cholesterol contents[a,b] mg	Tocopherol Content[b] I.U.
Norwegian cod liver oil[c] TWINLAB [c]	66-82	68-84	oil	-	-
Biosaumon (Medicorp[d] [France] [d] -Natural and without danger -No physicochemical processing	120	160	oil	NL	1
MaxEPA 300 (Walgreen Labs Inc.) -Hi potency omega-3 fatty acids -Cold water natural fish oil	180	120	oil	NL	NL
MaxEPA (Solgar Co., Inc.) -Marine lipid concentrate	180	120	oil	6 mg	L
Natural Omega-3 (Country Life) -Fish body oils[e]	180	120	oil	NL	10
Cardi-Omega-3 (Solar Nutritionals Inc.) -All natural MaxEPA fish oil concentrate	180	120	oil	5 mg	L
Your Life (P. Leiner Nutr. Prod. Inc.) -Natural fish oil concentrate	180	120	oil	CF	L
Proto-chol (E.R. Squibb & Sons Inc.) -Natural fish oils	180	120	oil	5-6	L
Natural brand Omega-3 (Sonergx Nutr. Prod.) -Fish oil concentrate	180	120	oil	NL	5
Nature's Best (Nature's Best Food Suppl.) -Natural fish oil concentrate	180	120	oil	5 mg	1
PROMEGA (Parke-Davis) -Natural fish oil concentrate	280	120	oil	<1	1
Super EPA 500 (Walgreen Labs Inc.) -Hi potency omega-3 fatty acids -Cold water natural fish oil	300	200	ethyl ester	NL	1
Cholesterex (Nutr. Prod. of Amer. Inc.) -Omega-3 fish oil concentrate -Purified natural fish oil concentrate	200	85	oil[f]	<3	L
Omega-'3' EPA SUPER 500 (Schiff Bio-Food Proc.) -Unsaturated fish oils[g]	300	200	methyl ester	NL	5
Health crafts EPA-Forte (Booker Health Products [U.K.]) -Selected marine lipid concentrate	310	210	ethyl ester	NL	L
PROMEGA PEARLS (Parke-Davis) – Natural fish oil concentrate	300 'omega-3' fatty acids per pearl[h]		oil	<1	<1

[a] CF = 'cholesterol free'; [b] NL = not listed, L = mentioned, amount not specified; [c] Vitamin A-1250 I.U., Vitamin D-130 I.U. per 500 mg capsule; [d] Vitamin A-700 I.U., Vitamin D-70 I.U. per 1 g; Includes garlic 50 mg and ascorbyl palmitate 2 mg, 'in a blend of glycerin, soybean oil, lecithin and lemon oil'; [f] Fat <1 g per serving of two capsules; [g] Willow bark 10 mg, included; [h] PEARLS softgel size is 600 mg. Values are given per softgel.

surprising to note (Table 2) that one oil product is described essentially as 300 mg of 'omega-3' fatty acids per 600mg gelatin capsule, presumably representing EPA and DHA plus 18:4n-3, 20:4n-3 and 22:5n-3.

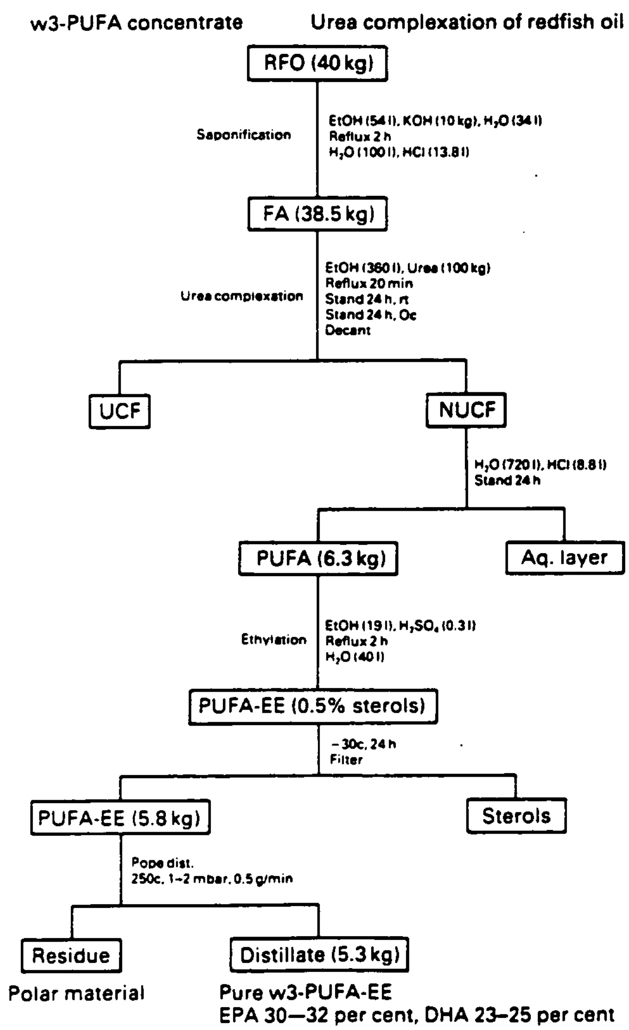
The latter fatty acid, DPA or docosapentaenoic [n-3] acid, is potentially of great biochemical interest. In the seal fat diet of the Greenland eskimos this fatty acid would have been quantitatively almost equal to DHA,[16-18] a fact reflected in the eskimo foods,[19] and in the blood platelet fatty acid analyses by Dyerberg and

Bang[20] with EPA shown to be 8.3 per cent, DPA 22:5n-3 3.4 per cent and DHA 6.1 per cent. Von Schacky and Weber have shown retroconversion of DHA to EPA in man, clearly via DPA.[21] Although DHA does not produce a known prostaglandin,[22] the role of DPA in the production of eicosanoids is as yet unknown. We are left with a basic problem regarding the eskimo diet – were the omega-3 fatty acid health benefits due to the megadose effects of total omega-3 fatty acids, or due to the distribution of these fatty acids on the glycerol of marine mammal fats, known to be different from that of fish oils,[16] or could the DPA content be a factor?

Why not vegetable oils?

The question of alpha-linolenic acid (18:3n-3) in our diets also gives ample room for speculation. Elongation and desaturation to EPA and DHA occur, but in man this process is slow. It is possibly even less effective in later years, and is affected by competition from the common dietary omega-6 linoleic acid (18:2n-6).[23-24] The effect of the increased consumption of leafy vegetables in salad form in North America as a source of 18:3n-3 is difficult to quantify, but two of the most popular vegetable oils, soybean and canola (low-erucic acid rapeseed oil) provide alpha-linolenic acid at 8-10 per cent of total fatty acids. Increased consumption of salad oils has become widely accepted as part of cholesterol-lowering diets, but they may also be influential in improving cardiovascular health in man through the contribution of alpha-linolenic acid.[25]

Fig 2 Flow scheme for concentration of fatty acids in commercial oil produced from redfish *(Sebastes sp.)* scrap by urea complexation, esterification, and short-path wiped-wall distillation



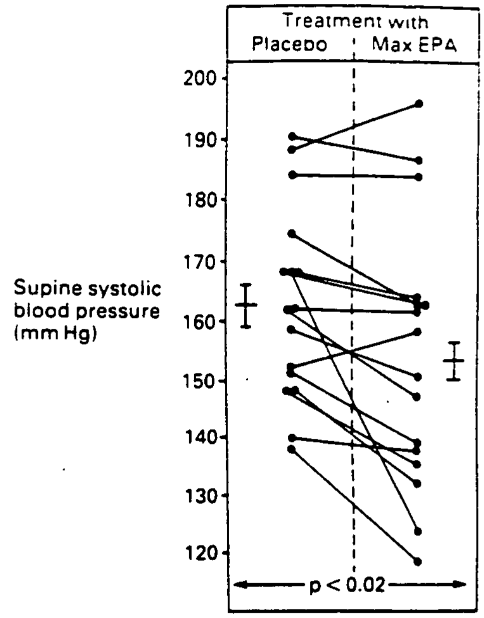


Fig 3 Individual patient changes in supine systolic blood pressure after initial treatment with placebos and after six weeks of fish oil capsules. Bars represent means and SEM[35]

Fish oils are an obvious source of longer chain omega-3 fatty acids (Table 1), but what about fish? The benefits of fish as sources of omega-3 fatty acids[6] have been promoted in innumerable articles in the popular press and fish as food has been promoted in books which have included topics on biochemistry and nutrition.[26,27] Two new and detailed tabulations of the composition of fish,[28,29] have just appeared to supplement established sources.[30]

Fish and shellfish as foods

Problems associated with high fish diets include variation in the fat content of any one species of fish, except for a few basic white fish species such as cod, haddock and saithe (pollock).[31] To achieve a meaningful intake of EPA and DHA in terms of therapy, instead of eating more fish as part of a varied diet designed to promote general health and reduce fat intake, is not easy. Table 3 shows that in an effort to achieve an intake of one gram of EPA and DHA a significant number of calories are

Table 3 **Comparison of weights of fish, with cholesterol and calories, necessary to provide 1 gram of EPA + DHA, with those of a typical fish oil concentrate**[a]

Diet component	Grams consumed per one gram of EPA + DHA	Cholesterol mg	Calories
Cod fillet (steamed)	500	185	410
Flounder (fried)	500	230	1070
Salmon (steamed)	100	74	199
Trout (steamed)	200	114	262
Crab (boiled)	250	195	317
Shrimp (boiled)	500	640	570
MaxEPA	3	14	30

[a] Calculations courtesy of S. Reed[32]

ingested with some typical fish and shellfish. Additional data on this point is presented elsewhere,[32] but it is pertinent[31] to rank most fish and shellfish as low to moderate (1-4 per cent) in fat, with salmon occupying a higher ranking with 6-9 per cent fat, and finally mackerel and herring at the highest level of fat content (10-20 per cent).

Obvious problems in the fatty species are rancidity, but it has been recorded that a daily intake of canned mackerel seems to be uniquely beneficial in elevated blood pressure.[33] On the other hand, in normal people this effect may not be observed.[34] Since we are discussing oils, it is not unreasonable that a supplement of MaxEPA should also be as efficacious[35] as fish, as shown in Fig 3. This is a not untypical result from the clinical treatment of humans with fish oils since genetic variability in man plays a large part in the scattering among the results.

Fish and shellfish are 'safe' to eat in most normal contexts, especially if cooked adequately.[36] Potent toxins of plant origin do enter into the consumption patterns of fish and shellfish in some parts of the world,[37] but in our lipid context it is instructive to look at two reports of mild digestive problems brought on by eating shellfish.[38,39] Phytoplankton are possible sources[40] of all of the fatty acids shown in Fig 4, and plants also contain lipoxygenases, so it is not surprising that one or more prostaglandins could be formed in sufficient quantity to have a local effect on the bowel muscles.

Some retail concentrates of omega-3 fatty acids

The range of fish oil concentrate products available 'over the counter', primarily in the USA, is shown in Table 2. The point of interest is that 'oils' are presumably triglycerides. In principle, one can concentrate oils by several means, starting with the simple winterisation or slow chilling of the oil. Menhaden oil can be enriched without solvent from 13.9 per cent EPA and 9.7 per cent DHA to 15.3 per cent and 10.9 per cent respectively.[31] The excess of palmitic acid (Fig 1) will aid in this process. With a nominal concentration of one EPA or one DHA per triglyceride molecule,[3] enrichment of triglycerides without enzymatic interesterification or resynthesis is not very practical beyond the 300 mg/g usually listed for these two fatty acids alone. By adding in other omega-3 fatty acids such as 16:4n-3, 18:4n-3, 20:4n-3 and 22:5n-3 it is possible to obtain a total of 500 mg/g.

Fig 4 Basic C_{18} polyunsaturated fatty acids of the omega-6 and omega-3 families, with C_{20} and C_{22} elongation products involved in prostaglandin biosynthesis[22]

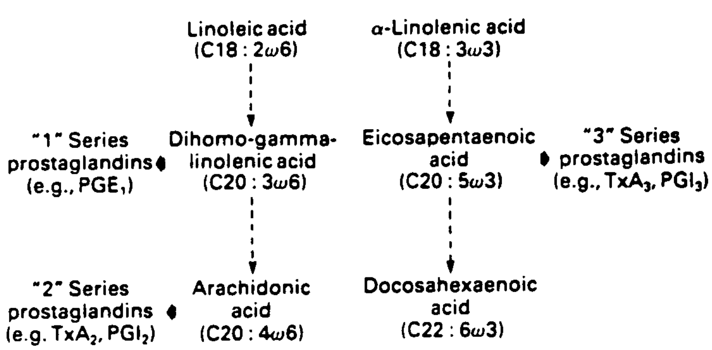


Table 4 **Urea enrichment of fatty acids (w/w per cent by GLC area) of redfish oil and concentrate compared with 'Ethive' concentrate product analysis of 1964 and with two contemporary retail products**

	Redfish oil[14]		Ethive[13]	Oil[a]	Ester[a]
Fatty acid	Starting oil	Urea concentrate		USA	U.K.
14:0	2.5	1.0	1.1	5.9	0.3
16:0	5.2	0.1	0.6	8.5	2.7
18:0	1.3	-	0.7	0.8	3.4
16:1	7.5	6.5	6.7	10.1	0.8
18:1	9.4	0.3	6.9	10.2	13.0
20:1	22.0	0.1	-	1.6	9.6
22:1	28.9	-	-	1.2	5.7
18:2n-6	0.4	1.2	3.1	1.2	0.5
18:3n-3	0.2	0.7	2.1	1.0	0.9
18:4n-3	0.8	5.1	6.1	4.6	2.9
20:4n-6	0.6	0.9	3.6	0.7	1.2
20:4n-3	0.3	1.6	?	1.1	1.9
20:5n-3	5.4	32.5	25.8	25.8	27.7
22:5n-3	0.8	3.0	4.7	1.8	3.7
22:6n-3	3.9	29.2	22.2	12.1	18.8

[a] R.G. Ackman, unpublished data

A simpler approach, and one increasingly apparent in this market, is to split the triglycerides into individual fatty acids (or their esters). These can be much more easily enriched in omega-3 fatty acids, for example by urea complexation as shown in Fig 2. Table 4 compares some of the main fatty acids of such a concentrate with the 'Ethive' composition mentioned earlier,[13] and two contemporary retail products.

Problems in refining and concentrating fish oil fatty acids

In our laboratory, in Nova Scotia, both an initial oil stripping to reduce polychlorinated biphenyl (PCB) content and a final purification of the ethyl ester product of the flow chart of Fig 2 are carried out with a Pope wiped-wall 'molecular' still (Fig 5). The main point to emphasise is that the short passage time of about a minute, limits the thermal abuse possible in some concentration techniques.

The extended exposure of alpha-linolenic acid at temperatures at or near 250°C produces geometric isomers.[41] The EPA and DHA are more sensitive. Figure 6 shows the EPA region of a gas liquid chromatogram of an ethyl ester concentrate produced in our laboratory, and the corresponding material as a distillate passed slowly through a Stedman packed column under a vacuum of about 1 mm with a pot temperature in excess of 230°C.

Polymerisation of EPA and DHA is another possible result of exposure of fish oils to oxygen, light or heat. Our laboratory employs an IBM-PC program to calculate the iodine value of the fatty acids in a gas liquid chromatogram. Since polymerisation may remove only one or two ethylenic bonds in an oil (Fig 7) leaving the rest to react with Wijs iodine value reagent, any difference greater than ± 5 IV units may be evidence of polymerisation.

A common misapprehension is that the areas of the peaks for the methyl esters of EPA and DHA, as percentages of the total volatile fatty acid methyl esters in a gas liquid chromatographic analysis, give the weight percentage of EPA and DHA in the sample. This is not at all the case and polymers are only one of the possible non volatile components,

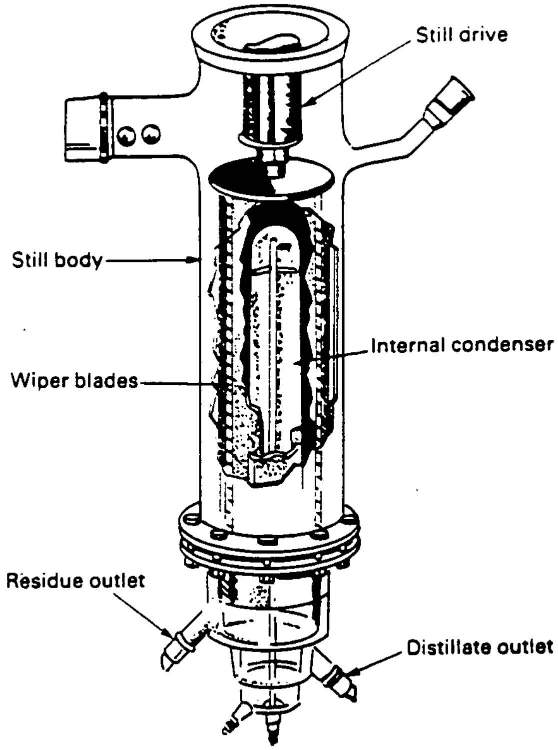


Fig 5 Cutaway view of main assembly of 152 mm diameter Pope wiped-wall molecular still. Courtesy of Pope Scientific, Inc., Menomonee Falls, WI, U.S.A.

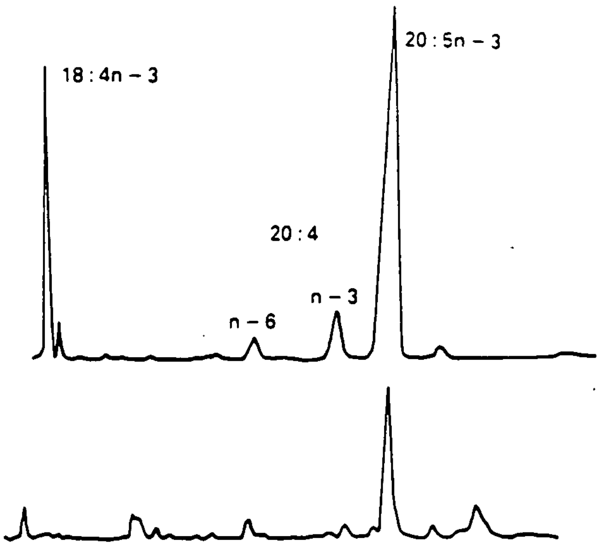


Fig 6 Comparison of gas-liquid chromatograms of ethyl esters of NUCF product from Fig 2 and after distillation through Stedman packed column. Note reduction in all types of polyunsaturated fatty acids and formation of new artifact fatty acids by prolonged heating at or near 250°C

which may include sterols, squalene, etc., while volatiles such as solvent residues in the sample can also give erroneous EPA and DHA proportions in the sample.

In Nova Scotia, we prefer to use methyl tricosanoate as an internal standard (Fig 8). This is the most reliable way to obtain the EPA and DHA contents of any sample of fish oil origin.[42] As an example, a concentrate submitted to us for analysis had a GLC w/w of 27.8 per cent for EPA and 23.9 per cent for DHA when area percentages were corrected for FID response.[42,43] The 'oil' therefore contained 27.8 × 0.95 = 26.4 and 23.9 × 0.95 = 22.7 g/100 g of fatty acids for EPA and DHA respectively, assuming that 5 per cent by weight was glycerol. The 23:0 internal standard showed that the EPA and DHA contents (or acids) were 22.1 and 19.2 g/100 respectively, or nearly 20 per cent less than indicated by the simple gas-liquid chromatography of all volatile methyl esters of fatty acids.

Delivering omega-3 fatty acids to the consumer

The soft gelatin capsule is an ideal and stable container for fish oils in the small amounts required for human consumption. MaxEPA capsules survived four years in the dark at ambient temperature with no obvious effect on the contents (peroxide value 1.9 meq/kg; polymer < 0.1 per cent by Iatroscan). However, light is a potent factor in autoxidation processes[44,45] for long-chain PUFA and should be avoided when storing fish oils or concentrates.

The gelatin capsules of fish oil and/or concentrates retailed over the counter usually contain a clear yellow 'oil', and as a sales point it is desirable to show this. Accordingly, the bottles of capsules are often in cardboard boxes, or are light-protected with a large label, and invariably use a heavily tinted glass or plastic bottle. Whether the added tocopherol (Table 2) has a valid effect during storage is open to question, as it is primarily a physiologically active antioxidant. However, it is good sales psychology.

The form in which the omega-3 fatty acids of fish oils are taken is soon to be a more controversial area. Alpha-linolenic acid, which has little effect on C_{20} and C_{22} blood fatty acids despite physiological benefits, can be absorbed as the ethyl ester,[24] as can the ethyl esters of fish oil concentrates.[46]

The increasing tendency to present fish oil fatty acids as ethyl esters (Table 2) is another way to possibly delay transfer into chylomicrons or other blood lipids.[16,47] Free fatty acids are not common in foods, but a few grams of fish oil concentrate taken in this form along with a meal should blend naturally into the complex processes[48] leading to fat absorption perhaps physiologically closer to the eskimo model.[16]

The omega-3 fatty acids are not drugs, do not necessarily give linear responses with dosage, and are always present in our blood fatty acids.[49] An 'overdose' is hardly likely, since PUFA are both catabolised steadily

Fig 7 Two modes of dimer acid formation in triglycerides based on polyunsaturated fatty acids usually found in the 2-glycerol position of marine fish oils. Cross linkages could be carbon-carbon or carbon-oxygen-carbon, and could also include 1- or 3-glycerol positions. Any unsaturated fatty acid could be involved but Rx and Ry are most probably 16:4n-3, 18:4n-3, 20:5n-3 or 22:6n-3

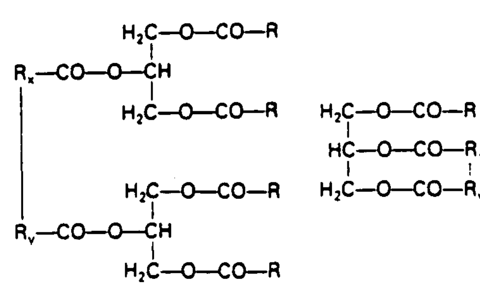


Table 5 Omega-3 fatty acids (in μg/ml) in serum lipids of two groups of healthy women. From Darioli *et al* [49]

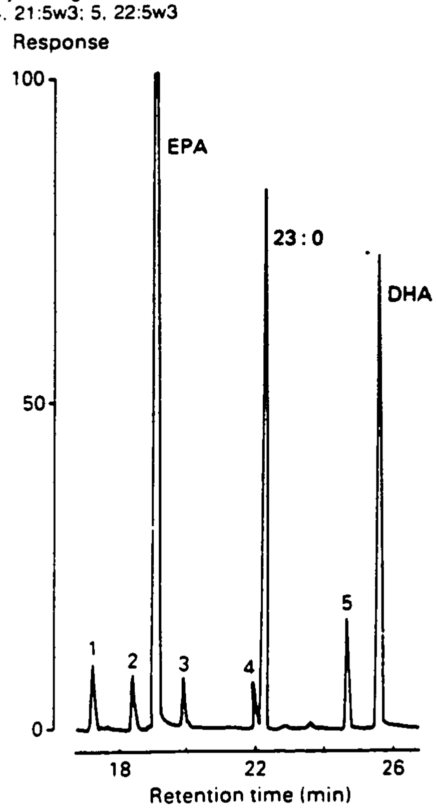
Fatty acid	Cholesterol esters		Triglycerides		Phospholipids	
	Cloistered	Control	Cloistered	Control	Cloistered	Control
18:3n-3	27.3	21.0	29.3	17.3	6.5	3.7
20:5n-3	35.6	30.3	6.8	5.2	28.7	25.6
22:6n-3	29.7	25.0	21.6	20.3	144.8	147.9

for energy or used for 'essential' metabolite production.[23] Table 5 shows some 18:3n-3, EPA, and DHA figures for blood lipids of two identified groups not on high fish diets. The omega-3 PUFA may function in body organs in ways not apparent from blood analyses. For example 18:3n-3 fed to pigs rapidly changes the EPA content of kidney phospholipids in a reversible way,[50] and the reversible effects of the long-chain omega-3 fatty acids of fish oils are one of the best assurances that they are in fact quite harmless.[51] The latter view is supported by epidemiological data from several countries where fish is widely eaten, and especially by the Zutphen study[52] where the risk of cardiovascular problems was reduced by fish consumption without any offsetting adverse clinical effects.

Thirty years of cholesterol research continue to generate conflicting views,[53] and the fact that in man fish oils moderate and reduce serum triglyceride more than serum cholesterol[54] means that fish oils are not yet readily accepted by many physicians for a health benefit role, although this attitude may be changing.[55] On the other hand, more than one million tons of fish oils are produced annually, in various parts of the world favouring local consumption patterns.

Fish and shellfish are actually not available in the quantities and qualities necessary to modify our diets on a large scale, desirable though this route to n-3 PUFA may be.[56] Compared to alternative therapies, capsules containing omega-3 fatty acids are readily accepted by patients,[35] and on a voluntary basis are also the basis of a thriving industry estimated to be worth nearly $200 million annually. Fish oils and/or fatty acids or esters, as concentrates, are the only practical means apparent in 1988 to supplement or modify the PUFA intake of a large section of the population in terms of EPA and DHA.

Fig 8 Partial gas chromatogram of marine oil fatty acid methyl esters showing EPA, 23:0 (tricosanoic acid: internal standard) and DHA with other closely eluting components. Peak 1, 20:4w6; 2, 20:4w3, 3, 22:1w11; 4, 21:5w3; 5, 22:5w3



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